

## Dendritic and Natural Killer Cells Cooperate in the Control/Switch of Innate Immunity

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Twenty years ago, R. Steinman and colleagues established that dendritic cells (DCs) have unique capacities to prime naive T cells and that DC maturation is the checkpoint for the initiation of adaptive immune responses (1–3). In the mid-1990s, C. Janeway pointed out the pivotal role of innate effectors in dictating adaptive immune responses while few researchers wondered why antigens were much more immunogenic for the specific immune system when applied with “adjuvants” that stimulated innate immunity (4). DC “maturation” appears to be the cornerstone between innate and cognate immunity, but what regulates DC maturation? DCs are sensors of infection and danger (5) and pathways leading to DC activation involve at least toll like receptors and/or proinflammatory cytokine and chemokine receptors (4, 5). However, in non-microbial scenarios such as tumorigenesis, transplantation, or atopy, DC activation might be regulated through other mechanisms whereby a third party cell could convey stress signals to DCs. The activated NK cell could be this third party cell, capable of directly triggering DC maturation (6, 7). In this issue of *The Journal of Experimental Medicine*, three articles shed some light on the regulatory role of NK cells on the control of DC functions (6–8).

The relevance of innate effectors such as NK cells in resistance to herpes viridae-related infections (9) and tumors (10) is being established. NK cell effector functions are regulated by the balance of activating and inhibitory signals transmitted by membrane receptors that recognize ligands on the cell surface of potential target cells (11–13). But which mechanisms contribute to the “priming” phase of NK cell activation? While so far, experimental model systems exploring NK cell recognition patterns used IL-2, a lymphokine downstream of T cell activation, there is a role for NK cells early on, before cognate T cell activation for the control of MCMV viral infections (9, 14, 15). It was proposed by Fernandez et al. (16) in a mouse model that DCs could act on the priming arm of innate immunity by triggering NK cell effector functions in vitro and in vivo in the setting of a tumor. In line with this observation, bone

marrow-derived DCs were shown to be pivotal for the control of hepatic mouse NKT cell activation (17). In this issue of *The Journal of Experimental Medicine*, three articles analyze the regulation of NK cell functions by DCs in human in vitro model systems (6–8) demonstrating that DCs can act on the priming phase of NK cell activation.

This commentary tries to highlight a few important links between the two players of innate immunity, DCs and NK cells, which may impinge on the course of immune disorders or translate into novel avenues for therapy.

*DCs and NK Cell Trafficking in Resting and Inflammatory Conditions.* The current concept of the multistep process of leukocyte recruitment into tissues envisions chemotactic agonists as key effector molecules (18). The rules governing DC trafficking are being unraveled, but much less information is available on the NK cell migratory pathways during homeostasis or inflammation. Rapid recruitment of DCs is a hallmark of inflammatory responses at mucosal surfaces (19) as documented after acute infection with bacteria or chronic inflammatory diseases (20). The migration and recruitment of NK cells from blood vessels to target tissues are the first steps in the cascade of events for NK cell activation. Indeed, after injection of MCMV (15) or MHC class I-negative tumor cells (14), a dramatic recruitment of activated NK cells at the inflammatory sites has been reported. Theoretically, both DCs and NK cells may be attracted to peripheral acute or chronic inflammatory sites by common sets of chemokines and could induce in auto-crine loops their reciprocal migration (21, 22). It is also conceivable that both DCs and NK cells could be directly recruited into lymph nodes from blood through high endothelial venules during inflammation, as recently demonstrated for monocytes, where a predominant role for monokines secreted in situ or in the periphery was highlighted (23). In contrast to the CD16<sup>+</sup> NK cell subset, CD16<sup>-</sup> NK cells respond most dramatically to the CC chemokine receptor 7 (CCR7) ligands (Epstein-Barr virus-induced molecule 1 ligand chemokine [ELC], secondary lymphoid tissue chemoattractant [SLC]) and CXC chemokine receptor 3 (CXCR3) ligands (IP-10 and ITAC) and express high levels of L selectin (24) potentially enabling them to reach lymph nodes. Nothing is known about a potential interaction between DC and NK cells in homeostatic resting conditions. The CD16<sup>+</sup>CD56<sup>+</sup> frac-

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tion of human resting peripheral blood NK cells express CXCR1 and CX3CR1, and respond to IL-8 and fractalkine, chemokines constitutively expressed in epithelia where immature DC accumulate (24).

However, comprehensive immunohistochemistry studies using novel and specific DC and NK cell surface markers are needed to validate the relevance of a DC/NK cell interaction in the course of homeostasis, acute and chronic inflammation.

*DCs as Surrogates for "NK Cell Stimulatory Factors".* The notion currently prevailing is that NK cells can be rapidly activated in the periphery by chemokines and/or inflammatory cytokines in conjunction with NK cell stimulatory factors such as IL-12, IFN type 1, or IL-2. However, NK cell stimulatory factors might not be readily available at the onset of acute inflammation. Indeed, in the case of IL-12 produced by DCs (5) or IL-2 secreted by polarized effector Th1 CD4<sup>+</sup> T cells, the adaptive arm of immune responses is typically required for such cytokines to be released. In viral infections where type 1 IFNs are produced, IL-12 secretion by DCs and NK cell responsiveness to IL-12 are both impaired (25). Moreover, virus-mediated antagonisms to cytokines and chemokines critical for NK cell activation have been described (26). So, in such circumstances of immune subversion, is there a surrogate pathway for NK cell activation, involving primarily the innate immune system? The pioneering work by Fernandez et al. (16) reported in a mouse tumor model that after Flt3L in vivo expansion or adoptive transfer of DCs into B6 mice, NK cell-dependent antitumor effects were observed, that were not accounted for by IL-12 nor IFN type 1. A role for CD8 $\alpha$ <sup>+</sup> DCs in the Flt3L-mediated NK cell-dependent antitumor effects was demonstrated, suggesting the capacity of DCs to activate NK cells. Bone marrow-derived DCs propagated in GM-CSF and IL-4 were electively capable of triggering NK cell IFN- $\gamma$  production and NK cell cytotoxicity in 18 h cocultures. A role for IL-4 in complete DC differentiation was outlined, as GM-CSF propagated DCs were not able to enhance NK cell lytic activity. In similar settings, classical NK cell targets (YAC-1 or P815-B7), when cocultured with NK cells, only trigger IFN- $\gamma$  production. In human in vitro systems, early studies pointed to a requirement for accessory HLA-DR<sup>+</sup> cells in NK cell killing of virally infected targets (27). Other groups made similar observations in human in vitro systems using CD34<sup>+</sup>-derived DCs or monocyte-derived DCs in coculture with IL-15-differentiated NK cells or IL-2-activated CD16<sup>+</sup>/CD56<sup>+</sup> NK cells (28, 29). In this issue, Piccioli et al. (6), Gerosa et al. (7), and Ferlazzo et al. (8) shed some light on the regulation of human resting NK cell activation by DCs.

Gerosa et al. (7) show that the cross-talk between immature DCs and resting NK cells leads to cell activation only in the presence of microbial stimuli. They demonstrate that resting fresh NK cells are activated by autologous or allogeneic DCs in the presence of concomitant inflammatory stimuli (LPS, IFN- $\alpha$ , mycobacterium tuberculosis). Upregulation of CD69, and enhancement of cytotoxicity against

Daudi, are hallmarks of CD3<sup>-</sup>CD16<sup>+</sup>CD56<sup>+</sup> NK cell reactivity after coculture with DCs in the presence of LPS. CD3<sup>+</sup> T cells do not respond to DCs subjected to LPS within 24 h. DC-mediated NK cell activation in the presence of LPS involves a cell to cell contact and neutralizing Ab anti-IL-2 or anti-IL-12 do not inhibit these effects. It is noteworthy that DC stimulation with LPS and not IFN- $\alpha$  allows NK cell IFN- $\gamma$  production, an effect associated with IL-12 production.

In the absence of microbial agents, Piccioli et al. (6) show that only when DC numbers predominate, i.e., conditions of a low NK:DC ratio, the DC/NK cell interaction results in NK cell activation (CD69 upregulation at 48 h DC/NK coculture).

Ferlazzo et al. (8) demonstrate that mature DC activated with a cocktail of inflammatory cytokines can promote human resting NK cell effector functions. However, in contrast to the other authors, they also show that immature DCs are capable of triggering resting NK cell functions at a low DC:NK ratio (1:10). This apparently conflicting result might be explained by the prolonged coculture periods used by the authors (7 d versus 24–48 h for the two other teams) and/or DC culture regimen (usage of 1% donor plasma for DC differentiation).

In as much as immature DC do not express MICA or ULBP-2 molecules, and as anti-NKp30 mAb do not prevent DC-mediated NK cell activation, a role for such NKG2D and NKp30 ligands seems unlikely (discussed in reference 8).

Altogether, these data stress that innate players, i.e., DCs can direct expansion (8) and effector functions (7, 8) of NK cells in the absence of exogenous adaptive-type (IL-2) cytokines.

*NK Cells Are Sensors of Danger for DCs.* Specialized antigen presenting cells such as DCs are sensors of "microbes" (5). Their activation leads to consequent increase in immunogenicity with delivery of signal 1 (peptide loading on MHC class I and II), of signal 2 (increased levels of costimulatory molecules), and signal 3 (polarizing cytokines). How do "bugs" trigger DC activation? (a) Direct activation of DCs via Toll-like receptors has been shown. Several toll-like receptors have been described on DCs, likely cooperating to widen the repertoire of recognition specificity, and triggering DC maturation in a nuclear factor (NF)- $\kappa$ B-dependent manner (4, 5). Heat shock proteins released by necrotic cells may also mature DCs and be considered as danger signals. (b) Indirect activation of DCs by signs of inflammation, i.e., proinflammatory cytokines (IL-1, IL-18, TNF- $\alpha$ ) and chemokines, is also NF- $\kappa$ B dependent. (c) In contrast to LPS-triggering, TREM-2/DAP12-induced DC maturation (30), like that initiated by the FcRs (31), is dependent on protein tyrosine kinase (PTKs) and extracellular signal-regulated kinase (ERK) signaling. TREM2/DAP12 engagement in DCs leads to upregulation of CCR7, CD40, CD86, and DC survival but not IL-12 nor TNF- $\alpha$  production. So far, TREM2/DAP-12 ligands remain unknown (30). (d) In situations where pathogens lack PAMPs, or during transplantation or tumor growth, is

there a role for a third party cell to convey “stress or bug” signals to DCs? NK cells can be turned on by IFN type I (viruses [9, 25]) or by inducible ligands for NK cell activating receptors, i.e., CD94/ NKG2D (tumors [10]) and could represent a first line of danger mediation.

In this issue, two articles demonstrate that activated NK cells promote DC maturation. In the absence of microbial stimulus, IL-2-activated NK cells can trigger activation of immature DC (upregulation of CD80, CD86, CD83, HLA-DR, CCR7) resulting in enhancement of DC allostimulatory capacity (6, 7). IL-2-activated NK cells dramatically boost IL-12 and TNF- $\alpha$  production by DCs in the presence of inflammatory stimuli. IL-2-activated NK cells induced DC maturation at a similar extent as LPS. It is of interest that IFN- $\alpha$  alone was almost inefficient at inducing DC maturation in the absence of NK cells, suggesting an IFN- $\alpha$ -mediated-positive feed back loop that augments both NK cell and DC activation. Activated NK cell-mediated DC triggering involves a cell to cell contact and partly soluble mediators such as IFN- $\gamma$  plus TNF- $\alpha$ , TNF- $\alpha$  playing a predominant role. Although activated T cells also induce DC maturation, NK cells are the only resting cell type within peripheral blood that can be readily and rapidly activated by IL-2 to mediate this function. TNF- $\alpha$  produced by DCs and IFN- $\gamma$  produced by IL-2-activated NK cells variably contribute to enhance induction of DC maturation. High concentrations of both TNF- $\alpha$  plus IFN- $\gamma$  synergized to induce DC maturation but never to the extent induced by IL-2-activated NK cells or LPS.

Gerosa et al. (7) also demonstrate rapid DC maturation triggered by NK cells activated by DCs. Indeed, after resting DC/NK encountering in the presence of IFN- $\alpha$  or other microbial agents such as LPS or mycobacterium tuberculosis, DCs upregulate CD86 and produce TNF- $\alpha$  and IL-12p40. In addition, Piccioli et al. (6) point to a critical role of the DC/NK cell ratio for optimal NK cell-mediated DC activation. Dealing with IL-2-activated NK cells, they demonstrate that, at low NK/immature DC ratios (1/5 and up to 1/40), the DC/NK cell interaction dramatically enhances (a) DC cytokine production (IL-12, TNF- $\alpha$ ) in a cell to cell contact-dependent manner, (b) DC maturation which was dependent on endogenously produced TNF- $\alpha$  (autocrine loop, membrane bound TNF- $\alpha$ ) and not on IL-12, IFN- $\gamma$ , IFN type 1, Fas, ICAM3, CD40L, CD80, CD86, and LFA1 (not shown). In contrast, in the absence of stress (IL-2, microbial agents), DC activation after NK cell interaction might be ongoing during overwhelming NK cell responses. Indeed, only a high NK/DC ratio leads to DC activation in resting culture conditions.

These data point to a critical role for NK cell activation in triggering DC maturation, therefore linking innate and cognate immunity.

*Turning Off Acute Immune Responses: NK Cells as a Control/Switch for DC Activation.* NK cells arrive at sites of infection within minutes to hours after pathogen invasion (9, 14, 15). Here they should encounter resident DCs already responding to signals derived from invading pathogens and proinflammatory cytokines. Given the ability of

activated DCs and NK cells to influence and recruit each other, a rapid influx of both DCs and NK cells will ensue. In this issue, Piccioli et al. (6) and Ferlazzo et al. (8) shed some light on the role of NK cells to shut off DC-mediated immune responses.

Piccioli et al. (6) show that the outcome between DC activation or death depends on the DC/NK cell ratio. At high NK:DC ratios (5/1), inhibition of DC functions is the dominant feature of the DC interaction with activated NK cells due to direct NK cell killing of immature DC. Indeed, both DC maturation and DC cytokine production (TNF- $\alpha$ , IL-12), observed at low activated NK/immature DC ratios (1/5 and up to 1/40), are abrogated at high NK:DC ratios. Ferlazzo et al. (8) demonstrates (versus mature DCs) elective killing of immature DCs by activated NK cells. NK cells, after activation by IL-2 or DCs, exhibit potent killing activity against immature DCs and secrete IFN- $\gamma$ . Activated NK cell lysis of immature DCs is blocked electively by anti-NKp30 Ab (and not by anti-NKp44, NKp46, NKG2D, 2B4, NKp80). In contrast, mature DCs are resistant to NK cell lysis. NK cells become capable of recognizing mature DCs in a NKp30-dependent fashion only in the presence of anti-MHC class I Ab.

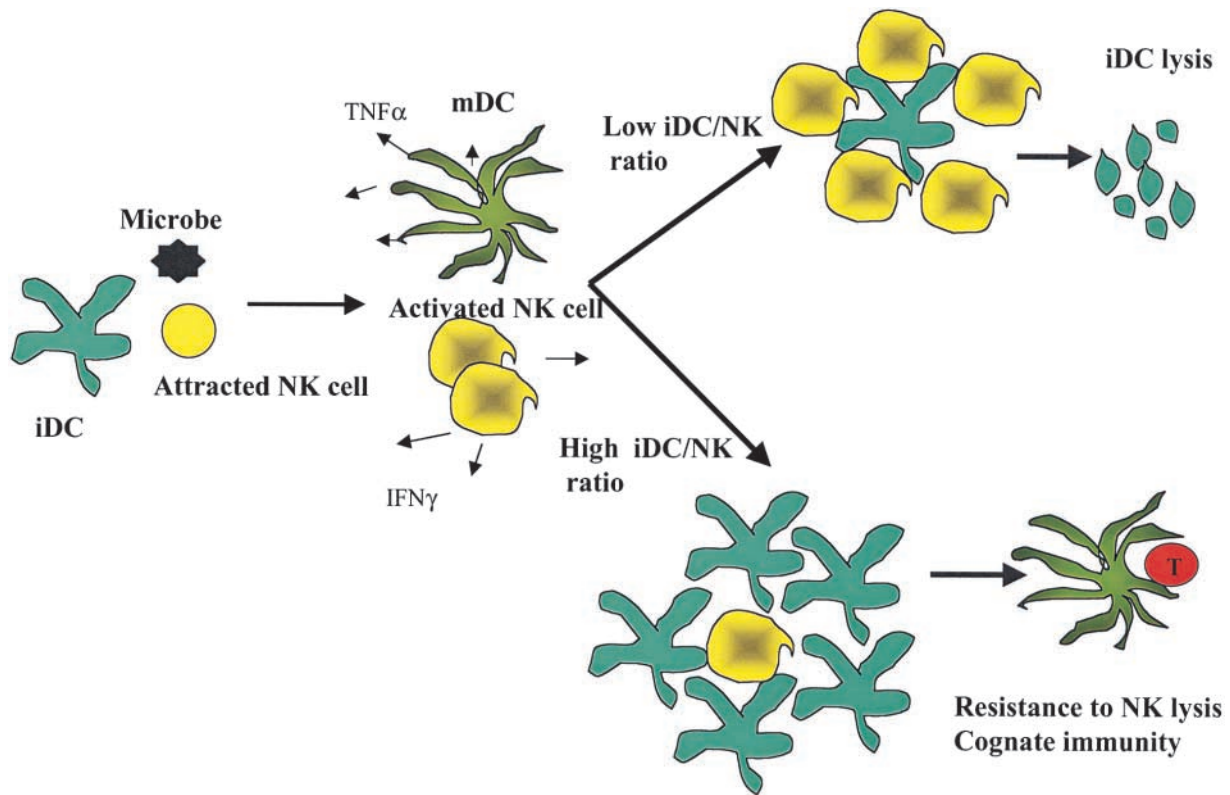
These data highlight a regulatory loop whereby DC-mediated NK cell activation leads to DC killing in case of overwhelming NK cell responses.

*Putative Scenarios in the DC/NK Cell Bidirectional Cross-talk.* In this issue, a bidirectional cross-talk between DCs and NK cells is described whereby DC-mediated NK cell activation and NK cell killing of DCs is the control/switch for DC activation or inhibition. This provides links between innate and cognate immune responses (Fig. 1).

After encounter with a pathogen or a danger, immature DCs mature and induce resting NK cell activation. NK cells are innate cytotoxic effectors but also regulatory cells releasing cytokines involved in innate resistance and adaptive immunity. They are required in resistance to Leishmaniasis for IL-12-mediated Th1 responses, in resistance to herpes viruses via IFN- $\gamma$  and/or cytotoxicity, in resistance to tumors expressing ligands for activating receptors, and in the regulation of B cell responses and autoimmunity (32).

Early at the onset of infection, before antigen-specific cognate T cells are expanded, NK cells become activated and amplify the maturation of DCs induced by microbial products or by virus-induced IFNs. Activated NK cells, by lysing target cells or surrounding immature DCs that have phagocytosed and processed foreign antigen, provide antigenic cellular debris internalized by maturing DCs that could be presented to T cells in lymph nodes. Thus, NK cells likely participate in DC-mediated cognate T cell responses. At later stages of immune responses, activated NK cells overwhelm surrounding DCs, the cross-talk between activated NK and DCs leads to NK cell-mediated DC death shutting off the antigen presentation.

The interaction between immature DCs and activated NK cells results in either DC maturation or cell death. The mechanisms that determine the outcome between death and maturation depend on a dynamics between DC and



**Figure 1.** Bidirectional cross-talk between DCs and NK cells. After encounter with a pathogen, immature DCs (iDC) secrete TNF $\alpha$  with or without IL-12, undergo maturation, and induce resting NK cell activation. The interaction between iDCs and activated NK cells results in either DC maturation or cell death. The mechanisms that determine the outcome between death and maturation depend on a dynamics between DCs and NK cell density and on the DC maturation stage. At high iDC/NK cell ratio, DCs become activated and resistant to NK cell lysis, enabling amplification of NK cell activation and elicitation of cognate immune responses. When NK cells are overwhelming, iDC-mediated NK cell lysis turns off local immune responses.

NK cell density and on the DC maturation stage. In addition, the cytokine pattern of DC activation after interaction with NK cells in response to various microbial stimuli could influence polarization of T cell responses. There might be physiopathological conditions whereby a disequilibrium of ratio between NK cells and DCs might result in aberrant cell activation (large granular lymphocytic leukemias associated with autoimmune disorders, Flt3L-mediated DC expansion).

The molecular basis of the DC-mediated NK cell activation remain unknown. A notion that emerges from these papers is that NK cells might need a “priming phase” of activation relying on recognition of DC ligands. This “priming phase” should be distinguished from the “effector phase” of NK cell activation, as receptors mediating DC or target recognition by NK cells (i.e., NKp30 NCR, CD40L, CD28) do not seem to be involved in the DC-mediated NK cell priming. DC/NK cell interaction might lead to upregulation of inducible NCR on NK cells (such as NKp44) or downmodulation of NK cell killer inhibitory receptor expression and/or engagement of critical costimulatory molecules (ICAMs, CD48, CD58). Indeed, NK cell function is mediated by the opposing effects of two sets of NK receptors defined operationally as activating or inhibitory receptors (11–13). Augmentation of antitumor effects

by specific NK cell inhibitory receptor blockade was demonstrated in vitro and in vivo (33). Based on the laws of NK cell alloreactivity, i.e., KIR epitope mismatching for HLA, Velardi’s group reported that killing of KIR epitope mismatched myeloid leukemias can be predicted by the lysis of corresponding normal blood cells and by specific HLA disparities (34). Delivery of positive signals through NK cell receptors does contribute to antitumor defense. Ectopic expression of ligands for NK cell activating receptors on tumor cells allowed NK cell-mediated tumor rejection in various mouse tumor models in vivo (8). Delivery of positive signals through NK cell receptors (Ly49H) was also relevant in anti-MCMV viral defense (15, 35). The study of the DC/NK cell immune synapse might shed some light on the supramolecular organization and potential intercellular transfer of MHC class I and/or ligands for NCR to the NK cell (36). Moreover, understanding the involvement of the non-redundant ITAM bearing polypeptides, i.e., CD3 $\zeta$ , FcR $\gamma$ , and KARAP-DAP12 in the DC-mediated NK cell activation might be instrumental for the characterization of the DC ligands (37).

Based on this novel DC/NK cell interaction, alternative NK cell-based immunotherapy strategies could be designed (unpublished data) that could substitute for the toxic systemic administration of NK cell stimulatory cytokines.

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